In response, applicant respectfully points out that (1) no Paper No. 9 has issued; (2) In Paper No. 6, applicant made election **with traverse** of Group III (claims 29-38); and (3) at the top of number paragraph 2 of the October 28, 1997 Office Action, the Examiner acknowledged "applicants' election with traverse of Group III (claims 29-38) in Paper No. 6."

Accordingly, applicant respectfully requests that the Examiner acknowledge that the election of Group III was made with traverse and note the record accordingly.

Objection to the Drawings

On page 2 of the October 28, 1997 Office Action, the Examiner objected to the drawings because of informalities.

In response, applicants will submit Formal Drawings in compliance with the April 16, 1997 Notice of Draftsperson's Patent Drawing Review, upon the indication of allowable subject matter.

Objection to the Title

On page 2 of the October 28, 1997 Office Action, the Examiner objected to the title of the invention because the title is not descriptive.

In response, applicants will amend the title if necessary, upon the indication of allowable subject matter.

Rejections Under 35 U.S.C. § 112.

In paragraph 7 on page 3 of the October 28, 1997 Office Action, the Examiner rejected claim 33 and objected to the specification under 35 U.S.C. §112, first paragraph because the specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention.

The Examiner stated that applicant has not provided sufficient guidance and direction nor objective evidence that the skilled artisan can deliver a therapeutic effective amount of Factor IX in an aerosol, oral or topical carrier in treating ischemic disorders. The Examiner stated that ischemia comprises treating vascular disorders and it would not be predictable that one could deliver a therapeutic effect amount in such disorders other than intravascular routes of administration. The Examiner stated that in the absence of objective evidence to the contrary; aerosol, oral and topical carriers and means of delivery are not enabled for treating ischemia.

The Examiner stated that pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 223 USPQ2d 1334 (PTO Bd. Pat App & Inter. 1992).

In response, applicant traverses the objection to the specification and traverses the rejection under 35 U.S.C. §112, first paragraph.

Applicant respectfully submits that use of aerosol, oral or topical carriers for delivering therapeutic effective amounts of compositions are known in the art. Applicant notes that the Examiner does not object to nor reject "intravascular" means of delivery for treating ischemia.

In regard to the Examiner's statement that "it would not be predictable that one could deliver a therapeutic effective amount in such disorders other than intravascular routes of administration," applicant herein provides references that demonstrate that many routes of administration may be predictably used to deliver therapeutic amounts in such disorders (See, Exhibits A-C).

Applicant respectfully submits that a variety of compositions, including aspirin and ticlodipine, are known in the art to be effectively delivered in therapeutic amounts by an oral route in such disorders. As an example, applicant directs the Examiner's attention to Exhibit A (Holdright, D., et al., 1994, Comparison of the effect of heparin and aspiring versus aspirin alone on transient myocardial ischemia and in-hospital prognosis in patients with unstable angina" J.Am.Coll.Cardiol. 24:39-45) for support that an oral route of administration may be predictably used to deliver therapeutic amounts in such disorders.

Applicant respectfully submits that a variety of compositions, including sevoflurane inhalation are known in the art to be effectively delivered in therapeutic amounts by an aerosol route in such disorders. As an example, applicant directs the Examiner's attention to Exhibit B (Rozdil'skaia, O.N., et al., 1993, The use of sodium nitroprusside aerosols combined with ultrasound in the combined treatment of patients with ischemic

heart disease and heart failure," Lik Sprava, 4: 97-100) for support that an aerosol route of administration may be predictably used to deliver therapeutic amounts in such disorders.

Applicant respectfully submits that a variety of compositions, including a nitroglycerin transdermal patch and thrombin-impregnated gauze, are known in the art to be effectively delivered in therapeutic amounts by a topical route in such disorders. As an example, applicant directs the Examiner's attention to Exhibit C (Todd, P.A., et al., 1990, Transdermal nitroglycerin (glyceryl trinitrate). A review of it's therapuetic use, Drugs 40:880-902) for support that a topical route of administration may be used predictably to deliver therapeutic amounts in such disorders.

Applicant respectfully submits that such publications evidence that applicant's disclosure was widely applicable and not limited as indicated by the Examiner. Furthermore, because such publications indicate that such routes of delivery do indeed have *in vivo* pharmacologic applicability, applicant respectfully submits that the Examiner misjudged the ability of one of skill in the art to deliver a therapeutic amount of the composition of the present invention in such disorder other than by the intravascular route. It has been so demonstrated.

Furthermore, applicant respectfully submits that the Examiner has miscast the rejections under 35 U.S.C. § 112, first paragraph. The Examiner's rejections and language closely track an improper utility rejection under 35 U.S.C. § 101. While a rejection properly imposed under U.S.C. § 101 should be accompanied with a rejection under 35 U.S.C. § 112, first paragraph, it is equally

clear that a rejection based on "lack of utility," whether grounded upon 35 U.S.C. § 101 or 35 U.S.C. § 112, first paragraph, rests on the same basis (i.e., the asserted utility is not credible).

The Examiner questions the correlation between an *in vitro* model and pharmaceutical or pharmacological treatment. However, a reasonable correlation is sufficient to be predictive:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a *reasonable* correlation between the activity in question and the asserted utility. The applicant does not have to prove that there is a statistically proven correlation between characteristics of a compound and the asserted use, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted.

MPEP 2107

Furthermore, data from *in vitro* and animal testing is generally sufficient:

> Data generated using *in vitro* assays and testing in animals almost invariably will be sufficient to support an asserted therapeutic or pharmacological utility. In *no* case has a Federal court required an applicant to support an asserted utility with data from human clinical trials ...[If] one skilled in the art would accept the animal tests as being *reasonably predictive* of utility in humans, they should be considered sufficient to support the credibility of the asserted utility. Examiners should be careful no to find evidence unpersuasive simply because no animal model for the human disease condition has been established prior to the filing of the application . . . [I]t is improper for an Examiner to request evidence of safety in the treatment of humans, or regarding the *degree* of effectiveness.

MPEP 2107

It is respectfully submitted that in light of the above-cited remarks and the exhibits, the presently claimed specification provides full support and teaching of how to make (and how to use) the presently claimed invention. In view of the foregoing, it is respectfully requested that the objection to the specification and the rejection of claim 33 under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C.§ 102(b)

In paragraph 10 on page 4 of the October 28, 1998 Office Action, the Examiner rejected claims 29-36 under 35 U.S.C. §102(b) as being anticipated by Moller et al. (CA 2,141,642). The Examiner stated that Moller et al. teach the use of factor IX which does not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods. The Examiner stated that the claimed functional limitations addressed by the applicant would be inherent properties of the referenced treatment of thrombotic disease resulting from life-threatening bleeding complications with factor IX.

In response, applicant respectfully traverses the rejection. Applicant respectfully reminds the Examiner that in order to maintain a rejection under 35 U.S.C. § 102(b), the cited prior art reference must disclose every limitation of the claim.

In response, applicant has herein above amended claim 29 to "chemically inactivated Factor IX." Applicant respectfully submits that the amendment obviates the rejection. In particular, Moller, et al. teach the use of **proteolytic fragments** of factor IX, 12-15 kD, which **are not chemically modified**.

Moller, et al. do not disclose a **chemically modified** factor IX. Thus, the cited prior art reference, Moller, et al., does not disclose every limitation of the presently claimed invention.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection, and allow the pending claims, namely claims 29-38.

Applicant notes that claims 37-38 were not rejected under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103(a)

The Examiner stated that claims 29-37 are rejected under 35 U.S.C. § 103 as being unpatentable over Moller et al. (CA 2,141,641) in view of standard methods of inactivation on page 17 of the instant specification and in view of known ischemic disorders on page 16 of the instant specification. The Examiner stated that the instant claims are drawn to treating ischemic disorders with inactivated Factor IX.

The Examiner stated that Moller, et al. teach the use of factor IX which does not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods. The Examiner stated that by teaching factor IX with no coagulation activity, it would have been obvious to an ordinary artisan to inactivate factor IX by known methods to generate a factor IX that does not have coagulation activity but that can interfere with thrombosis. The Examiner stated that by teaching treating thrombotic diseases encompassed by the claimed methods, it would have been obvious to treat other ischemic disorders encompassed by the claimed methods because inhibiting the coagulation cascade and thrombosis as taught by Moller et al., would have been

expected to inhibit vascular complications and thrombosis associated with ischemia associated with the conditions set forth in claims 36-37. The Examiner stated that it was known at the time the invention was made that ischemia or deprivation of oxygen was due, in part, to coagulation or thrombosis and that the treatment of such conditions relied upon anti-coagulants. The Examiner stated that the dosage range and routes of administration (intravascular) were all known at the time the invention was made and would have depend upon the needs of the subject for a particular ischemia disorder.

The Examiner stated that one of ordinary skill in the art at the time the invention was made would have been motivated to select factor IX as an anticoagulant to treat ischemic. The Examiner stated that from the teachings of the reference and of that known and practiced by the ordinary artisan, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references, especially in the absence of evidence to the contrary.

In response, applicant traverses the rejection. Applicant respectfully submits that the amendment to claim 29 made herein above adequately addresses the Examiner's concerns. Applicant also notes that claim 38 is not rejected under 35 U.S.C § 103.

Furthermore, applicant respectfully submits that the cited prior art do not provide (1) all of the elements and limitations of the presently claimed invention or (2) the reasonable expectation of success, as required to make a *prima facie* case for obviousness

under 35 U.S.C. § 103(a) for the invention as presently claimed. Moller, et al. offers no suggestion to use "chemically" modified factor IX. Indeed, Moller, et al. teaches away from the use of chemically modified factor IX.

In particular, on page 4, lines 11-18, and on page 5, lines 5-9, Moller, et al., state that the "proteolytic fragments **are not chemically modified**." (emphasis added). Moller, et al. further direct that "fragments shouldn't be chemically modified." (See page 9, lines 1-2). Moller, et al. note that an advantage of their invention is "avoidance of a chemical modification of factor IX fragments." (See page 10). Moller, et al. exemplify their invention using various proteolytic cleavage techniques. (See Example 1, Example 2, Example 3, and Example 4). Therefore, relying on Moller, et al., one of skill in the art would not have a reasonable expectation of success using chemical modification of factor IX fragments.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a) and allow the claims, namely claims 29-38.

SUMMARY

In view of the preceding amendments and foregoing remarks, applicants maintain that the subject application is now in condition for allowance. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection set forth in the October 28, 1997 Office Action and earnestly solicit allowance of all claims now pending in the subject application, namely claims 29-38.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

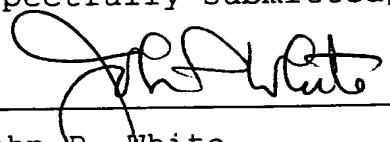
In accordance with the duty of disclosure under 37 C.F.R. §1.56 in connection with the above-identified application, applicant respectfully directs the Examiner's attention to the following reference which is listed on Form PTO-1449 attached hereto as Exhibit D. A copy of the cited reference is attached hereto as Exhibits E.

1. Benedict, C.R., et al., 1994, Endothelial-Dependent Procoagulant and Anticoagulant Mechanisms, Texas Heart Institute Journal 21:86-90 (attached as Exhibit E).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

No fee, other than the $475.00 fee for a three month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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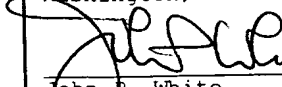

4/25/98

John P. White
Reg. No. 28,678

Date